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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
VASG-P02-003	

Application Number	Filed
09/487,023	January 19, 2000
First Named Inventor	
Gill et al.	
Art Unit	**Examiner**
1635	S. McGarry

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 54,144
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

Signature

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Telephone number

March 7, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 3/7/08 Signature: Elaine Leahy (Elaine Leahy)

Docket No.: VASG-P02-003
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gill et al.

Application No.: 09/487,023 Confirmation No.: 2622

Filed: January 19, 2000 Art Unit: 1635

For: METHOD AND COMPOSITION FOR TREATMENT OF KAPOSI'S SARCOMA Examiner: S. McGarry

REMARKS ACCOMPANYING PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated September 7, 2007, Applicants respectfully request that a panel of examiners review the pending rejections. Applicants enclose the requisite Notice of Appeal, Pre-Appeal Brief Request for Review, a Petition for a three-month extension of time, and appropriate fees. Please consider the remarks below which accompany Request form PTO/SB/33, filed herewith.

REMARKS

Claims 2, 9-12, 16, 20, 24, and 25 remain rejected under 35 U.S.C. § 103(a). Independent claim 2 recites an antisense oligonucleotide directed against VEGF, wherein said antisense oligonucleotide comprises a plurality of phosphorothioate moieties and has a sequence selected from the group consisting of SEQ ID NOs: 9-18, 20-21, and 28-29, and wherein said antisense oligonucleotide inhibits proliferation of Kaposi's Sarcoma cells. Independent claim 16 is directed to a pharmaceutical composition comprising the antisense oligonucleotide of claim 2.

The Examiner alleges that the pending claims are unpatentable under 35 U.S.C. § 103(a) over Uchida et al. (US 6,150,092, herein "Uchida"), and Robinson et al. (US 5,814,620; 5,710,136; 5,801,156, herein "Robinson") for the same reasons set forth in the Office Action mailed July 11, 2006. Specifically, the Examiner maintains that Uchida taught the region defined by SEQ ID NO: 7, to which allegedly all of the

claimed oligonucleotides are targeted, as a desirable region for targeting VEGF with antisense. In addition, the Examiner asserts that Robinson demonstrated targeting VEGF with antisense to be useful in various methods of treatment. It is further alleged that both Uchida and Robinson taught phosphorothioate modifications of VEGF antisense oligonucleotides. As such, the Examiner contends that one of ordinary skill in the art "would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF" and that "[o]ne would clearly look to the SEQ ID NO: 7 region in the making of antisense targeted to VEGF" taught by Uchida since it has been shown to be an effective target region.

Applicants respectfully disagree and submit that the pending claims are not obvious in view of the cited references for at least the following reasons.

First of all, the claimed invention relates to a few *particular* VEGF antisense oligonucleotides (e.g., SEQ ID NOs: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29). Although Uchida discloses hundreds of antisense oligonucleotides, Uchida does not disclose any of the claimed nucleotide sequences, let alone any modified form of these nucleotide sequences (e.g., "comprising a plurality of phosphorothioate moieties" as recited in claim 2). Contrary to the Examiner's assertion, Uchida teaches a much larger "core region" than SEQ ID NO: 7. Uchida's core region spans at least about 500 nucleotides in the VEGF gene (see the paragraph bridging columns 20 and 21), including regions within the 77- to 570-positions in SEQ NO: 1, the nucleotide sequences of from the 95- to 108-positions (SEQ ID NO:2), 149- to 174-positions (SEQ ID NO:3), 185- to 210-positions (SEQ ID NO:4), 219- to 244-positions (SEQ ID NO:5), 254- to 276-positions (SEQ ID NO:6), 287- to 328-positions (SEQ ID NO:7), 357- to 372-positions (SEQ ID NO:8), 389- to 534-positions (SEQ ID NO:9), SEQ ID NOS:2, 4, 5, 6, 7, and 9 (see column 21, lines 34-49).

The teachings of Uchida at best disclose a *genus* of VEGF antisense oligonucleotides which target the large "core region" spanning over 500 bps, while the claimed invention essentially constitutes a *species* invention. MPEP 2144.08, Section II.A.4 sets forth the guideline for determining whether a claimed species is obvious in view of a prior art genus: "[i]n light of the findings made relating to the three *Graham* factors, Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., Ochiai*, 71 F.3d at 1569-70, 37 USPQ2d at 1131; Deuel, 51 F.3d at 1557, 34 USPQ2d at 1214 ('[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art.' (emphasis in original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901; *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ('The prior art must provide one of ordinary

skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.')...To address this key issue, Office personnel should consider all relevant prior art teachings, focusing on" (where applicable) (a) the size of the genus, (b) the express teachings, (c) the teachings of structural similarity, (d) the teachings of similar properties or uses, (e) the predictability of the technology, and (f) any other teaching to support the selection of the species or subgenus.

Applicants submit that the claimed species invention is not obvious in view of Uchida's genus disclosure because Uchida provides no teaching or suggestion to select the claimed species sequences. Regarding the "size of the genus" factor, a skilled artisan would know that Uchida's genus disclosure of the "core region" (over 500-bp in length) encompasses at least thousands of species antisense sequences directed to this "core region," considering that each antisense oligonucleotide may differ from each other by at least one nucleotide and by length. By contrast, the claimed invention only relates to a few specific species sequences. The large size of the genus clearly favors the non-obviousness of the claimed invention, particularly in the absence of any teachings of Uchida to select the claimed species. Regarding the "teachings of similar properties or uses" factor, Applicants note that it is the instant specification that discloses the unexpected and unique result of achieving substantial inhibition of cancer cell proliferation in cultured cells and in animal models (see, e.g., Examples 3-7 and 9-11 on pages 19-28). Finally, the "predictability of the technology" factor also favors non-obviousness in this case. Antisense technology was well known for its unpredictability. Indeed, VEGF antisense oligonucleotides differing by one or two nucleotides exhibit significantly different activity in inhibiting VEGF expression. For example, Uchida's Table 2 shows that although A473J differs from A473I by a single nucleotide, there is an about 50-fold difference in their activities. Also, Applicants' specification discloses that although SEQ ID NOs: 8 and 9 differ by two nucleotides, there is an about 10-fold difference in their activities (see Table 1 on page 24).

Although the Examiner appears to focus on the "structural similarity" factor, by considering all the relevant factors, the totality of the circumstances strongly favors the non-obviousness of the claimed species invention. Given that the claimed antisense probes (either unmodified or modified) are not disclosed literally or inherently in Uchida, it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida any teaching or motivation to make these particular sequences and to further modify the oligonucleotides with PS. The other cited references (Robinson) fails to provide any sequence that is identical or similar to the claimed sequences; the defects of Uchida are not cured by Robinson.

Secondly, the cited references, either singly or in combination, do not teach the claim limitation – "wherein the antisense oligonucleotide *inhibits proliferation of Kaposi's Sarcoma cells.*" Although the Examiner argues that Uchida inherently teach this claim limitation, Applicants respectfully disagree.

Inherent characteristics cannot be obvious to one of ordinary skill in the art. MPEP 2112 points out that "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Given the unpredictable nature of antisense technology, a skilled artisan would appreciate that Uchida's antisense sequences do **not necessarily** inhibit proliferation of Kaposi's Sarcoma cells because of their sequence variations from the claimed sequences. As such, Uchida fails to teach each and every limitation of the claimed invention, even if combined with Robinson.

Thirdly, Applicants traverse the Examiner's assertion that Uchida would motivate one of ordinary skill in the art to test a myriad of probes within the region corresponding to Uchida's SEQ ID NO:7 so as to arrive at the presently claimed probes, and, further to modify those probes for use in vivo (*e.g.*, by introducing phosphorothioate moieties). As Applicants argued in the Responses filed on May 19, 2004 and August 5, 2005, Uchida discloses unmodified antisense probes that are effective in decreasing VEGF expression in cell-free assays (e.g., Uchida et al., Tables 1-8). Although Uchida briefly describes cell-based assays with PS-modified forms of antisense probes, these PS-modified probes did not work well in cells. For example, Table 9 of Uchida et al. clearly shows that the amount of VEGF expression in the presence of the PS-modified probes remained high, ranging from 54% to 70% of normal (59% to 82% when corrected for the baseline inhibition seen in the controls). It was known in the art that phosphorothioate modifications are employed only when an antisense probe is intended for use in cells. Given the ineffectiveness of Uchida's probes in cells, Uchida would not render obvious the claimed phosphorothioate modified probes.

The ineffectiveness of Uchida's probes to inhibit VEGF expression in cells is further substantiated by the Declarations from Dr. Parkash Gill and Dr. Dr. Ruiwen Zhang (submitted on August 5, 2005). As experts in the field of antisense technology, both Dr. Gill and Dr. Zhang concluded that Uchida's data shows that the tested probes of Uchida are *not effective* for inhibiting VEGF expression in cells. Moreover, on the facts presented to Applicants through these Declarations, Uchida's data would tend to *discourage* one of ordinary skill in the art from developing antisense probes against the region of SEQ ID NO:7, because the skilled artisan would conclude that such probes had been ineffective. Uchida, by in fact demonstrating the ineffectiveness of probes targeted to SEQ ID NO:7, teaches *away* from the development of the claimed probes.

However, the Examiner dismissed these two expert declarations as mere opinion. Applicants respectfully disagree. Applicants note that Uchida's characterization of his own data is also merely opinion. Gill, Zhang, and Uchida have all looked at the data presented and reached different conclusions. The Examiner must decide which evidence is more credible. Applicants note that it is common for Examiners to

dismiss as per se not credible the declarations of inventors pertaining to the patentability of their own inventions. Uchida's interpretations of his own data presented in an application for patent should be viewed with the same suspicion. By contrast, Applicant is not aware that Dr. Zhang has any interest one way or the other in the outcome of the present prosecution. Therefore, Applicants request that the Examiner reconsider the credibility of the evidence before him.

According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195 at pages 57,526-57,535) (effective October 10, 2007) ("the Guidelines"), a § 103 claim rejection based on a purported teaching, suggestion or motivation to combine prior art references to arrive at the claimed invention must support a conclusion of obviousness by including: (1) a finding that there was some teaching, suggestion or motivation to modify or combine the cited references; (2) a finding that there was a reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary in view of the specific facts. In this case, in view of the arguments above, the Examiner has provided no rational basis, explicit or implicit, to support a legal finding of obviousness. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. If there are any other fees due in connection with the filing of this submission,, please charge our **Deposit Account No. 18-1945**, under Order No. **VASG-P02-003** from which the undersigned is authorized to draw.

Dated: March 7, 2008

Respectfully submitted,

By _____

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